

## MARKED-UP VERSION OF CLAIMS

1. (Amended) A pharmaceutical composition comprising 1.5--6.9 % (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane, and [3~18 %] 3 ~ 18 % (w/v) of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, polyvinyl--pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium[,] alginate, N--2- hydroxypropylacrylamide, ethylene epoxide-polypropylene glycol, pectin, [mannitol,] and pentahydroxyethylstarch; as well as the remainder of conventional injections, as long as sodium chloride is not less than 1. 5 % (w/v), and the concentration of sodium ion is not more than that of 6.9 % (w/v) sodium chloride solution or equivalent.

4. (Twice Amended) The pharmaceutical composition of Claim 1, wherein said hydroxyethylstarch contains at least 10% hydroxyethylstarch with a molecular weight of 25,000--45,000 atomic mass units.

5. (Amended) The pharmaceutical composition of Claim 1, wherein said gelatin derivatives have a molecular weight of 20,000~35,000 atomic mass units, and are selected from urea--conjugated gelatin, modified liquid gelatin, oxidized polygelatin and degraded gelatin polypeptide.

6. (Amended) The pharmaceutical composition of Claim 1, wherein said dextran has a molecular weight of 40,000--230,000 atomic mass units; said carboxymethylstarch has a molecular weight of 30,000--80,000 atomic mass units, said PVP has a molecular weight of 5,000--700,000 atomic mass units, said condensed glucose has a molecular weight of 8,000~12,000 atomic mass units, said sodium alginate has a molecular weight of 20,000--26,000 atomic mass units, said pectin has a molecular weight of 20,000~40,000 atomic mass units; and said pentahydroxyethylstarch has a molecular weight of about 264,000 atomic mass units.

7. (Amended) A method for preparing the pharmaceutical composition of Claim 1, comprising:

dissolving 3--18g of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, PVP, gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N--2--hydroxypropylacrylamide, ethylene epoxide-polypropylene glycol, pectin, [mannitol,] and pentahydroxyethylstarch, in total of 100 ml of one injection or mixture of several injections selected from water [for injection], physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution;

[the] adding 1.5g sodium chloride and 0—5.4g of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate, and Tris [with the proportion described above],

[then] mixing[,] to dissolution [dissolving,] to obtain said pharmaceutical [the] composition [of the present invention].

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**Novel Pharmaceutical Compositions for Treating and Saving IN THE  
UNITED STATES PATENT AND TRADEMARK OFFICE  
**and the Method for the Preparation thereof****

5

**SPECIFICATION**

**accompanying**

**Application for Grant of U.S. Letters Patent**

10

**TITLE: NOVEL PHARMACEUTICAL COMPOSITIONS FOR TREATING AND SAVING AND  
THE METHOD FOR THE PREPARATION THEREOF**

15

**FIELD OF THE INVENTION**

The present invention relates to a novel pharmaceutical composition for treating and saving the wounded, and to a method for the preparation thereof. **[0001]** Nowadays blood transfusion and fluid infusion are the important measures to treat and save the wounded persons, especially thepersons suffering from traumatic shock. Usually, the principle of transfusion is “to infuse ~~component~~ components the patient is deficient in, to supply how much the patient needs”. For example, when the patient has mainly lost ~~his~~ blood, he should be transfused with blood, even though sometimes the patient needs to be transfused with blood from normal individuals. When the patient has mainly lost plasma, plasma or plasma volume expander should be transfused to him; ~~when.~~ When the patient has mainly lost intercellular fluid, physiological saline should be infused. In fact, the treating and saving measures of formulating physiological solutions on the basis of normal body composition ~~of body~~, or transfusing with blood from normal individuals to

20

25

30 the patient with evident physiopathological changes is to treat the organism

as a mechanical device, therefore these measures often have the following disadvantages:

[0002] (1) Blood transfusion: In general, the volume of blood ~~transfusion~~  
~~else~~transfused comes close to or exceeds the volume of blood lost. If a big  
5 amount of blood is required, the blood source will be difficult to obtain, the  
cost ~~is~~will be expensive. ~~The, and its~~ preparation and storage ~~need~~require  
certain conditions. In addition, before transfusion, some time should be taken  
for blood typing and cross match tests, and only the substitutes could be used  
for the individuals with rare blood types. Blood transfusion could result in  
10 production of anti--platelet antibodies and anti--~~leucoocyte~~leukocyte  
antibodies, as well as various hematogenic infectious diseases, for example,  
AIDS, hepatitis B, hepatitis C. etc.

[0003] (2) Albumin infusion: There is a great demand, a great expense  
~~difficult, difficulty in obtaining a~~ source, complicated preparation method,  
15 and certain requirements for, the method of storage of albumin. After  
albumin infusion, it could effuse through capillaries, and couldn't be  
reabsorbed into vessel. Therefore interstitial edema will occur, and might  
result in pulmonary edema, renal failure, and cardiac insufficiency, ~~by~~  
~~contrast enhance~~thus enhancing the possibility for mortality. Albumin  
20 infusion could result in evident decrease of  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ,  $\gamma$ -globulins and  
fibrinogen, cause reduction of immunity, and affect function of blood  
coagulation.

[0004] (3) Infusion of fluorocarbon as plasma substitute: ~~It~~Such infusion  
requires a large amount of the substitute and simultaneous inhalation of  
25 oxygen with high component pressure. ~~Otherwise~~Otherwise the demand of the  
organism is not met. The fluorocarbon as plasma substitute should be  
preserved ~~in~~at a low temperature, and its transport is not convenient. For  
example, thirty minutes before infusion, the patient should be injected with 10

mg of dexamethasone. The frozen injection for infusion should be thawed. Thus, the procedures are complicated. After infusion, ~~the~~ observation should be continued for 5 ~~—10—~~ 10 min. The infusion of fluorocarbon as plasma substitute could induce adverse reactions, such as anaphylaxis, hypotension, 5 thrombocytopenia, hepatosplenomegaly, reduction of immunity, and abnormality of fibrinolysis system.

**[0005]** (4) Infusion of balanced buffers, ~~Its~~. The amount of balanced buffers infused should be three times more than the volume of blood lost to maintain the blood pressure. 60--80% of the solution infused could effuse out of the 10 blood vessel, which results in tissue edema (for example, cerebral edema, pulmonary edema) and renal insufficiency, ~~it~~ which in turn could cause the difficulty for sequential therapy.

**[0006]** (5) Infusion of physiological saline. ~~Its~~ The amount of physiological saline infused should also be three times more than the volume of blood lost. 15 Its efficacy is poorer than balanced buffers, and its adverse effects are more significant.

**[0007]** To solve the problems in blood transfusion and infusion, the skilled in the art had studied anti--shock therapy with hypertonic sodium chloride solution. For example, 7. 5% (w/v) NaCl solution as suggested by Velasco. 20 ~~But the~~ The hypertonic NaCl solution, however, has some toxicity to the organism.

**[0008]** Most investigators have proposed intravenous injection of hypertonic NaCl solution for anti--shock therapy, but it usually leads to obvious complications, such as hypotension, rupture of blood cells induced by extra 25 hypertonic solution, cardiac insufficiency, decreased renal function and disorders of the nervous system.

**[0009]** Thus, it can be showed that there is a demand for novel anti--shock drugs to reverse the physiopathological condition of shock, in order to obtain

time for sequential therapy after the emergency treatment, and to create opportunity ~~with~~for improved effect of treating and saving the wounded and patients, and ~~with increased~~increasing survival rate.

5 **[0010]** An object of the present invention is to provide a pharmaceutical composition with a convenient source, that requires less dosage, and that has rapid and better efficacy, less side effects, wider uses, ~~and without restriction~~is not restricted by blood type ~~as well as without~~and does not require special storage ~~condition~~conditions.

10 **[0011]** Another object of the present invention is to provide ~~the~~a method for the preparation of the said pharmaceutical composition.

**[0012]** The present invention proposes a new concept of liquid therapy for shock, based on three aspects of thinking. The first aspect ~~in connection with~~relates to the present unreasonable dosage regimen, and adopts the following principle ~~is adopted~~: "to infuse what component the patient needs, 15 then to infuse how much the patient needs". Based on the physiopathological status of the patient with shock, there is a prior demand for the compound solution containing hypertonic sodium ion (or combination of various crystals, or combination of various crystals and various colloids, etc.) to preliminarily improve micro--circulation, tissue perfusion, and 20 hemodynamics immediately. Then in the light of practical demand the isosmotic solution or proper hypoosmotic solution or whole blood or concentrated red blood cell suspension is administered, in order to permit the latter infused solution better action when the patient's condition has improved preliminarily by the earlier hypertonic solution, and to remit over-- 25 dehydration of some cells caused possibly by the hypertonic solution infused earlier. The second aspect, ~~in connection with~~relates to the present unreasonable ratio of colloids and crystals in the transfusion for patient with shock when prepared on the basis of their normal physiological

concentrations, ~~in.~~ In view of the fact that the property and volume--expanding ability of artificial colloids are different from albumin in blood, it is considered that the transfusion with suitable ratio of colloids and crystals; ~~instead of human normal physiological proportion;~~ should be administered on  
5 basis of the physiopathological status of patients, rather than the, ~~instead of human normal physiological proportion.~~ Thus medicine administration according to indications could reduce the dosage, increase the efficacy, and decrease the complications. The third aspect, ~~in connection with a lot of~~  
10 relates to inadequacy in the present anti--shock experimental studies (such as animal model, reasonable concentration and infusion rate of hyperosmotic solutions), a great number of experimental studies have been conducted, and met with success.

**[0013]** Based on the above three aspects of thinking ~~form~~from the theoretical researches and the clinical experiences, the particular embodiments of the  
15 present invention have been completed through ~~the~~ animal experiments and ~~the~~ clinical practice.

**[0014]** The present invention is achieved through the following embodiments. A pharmaceutical composition comprising 1.5—6.9% (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate,  
20 potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane; and 3--18%(w/v) of one or more substances selected from hydroxyethylstarch, dextran, carboxy methylstarch, polyvinyl- pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose,  
25 glycerin, xylitol, sodium alginate, N-2- hydroxypropylacrylamide, ethylene epoxide--polypropylene glycol, pectin, mannitol, and penta hydroxyethylstarch (Pentastarch) as well as the remainder of conventional injections, as long as sodium chloride is not less than 1. 5%(w/v), and the



concentration of sodium ion is not more than that of ~~in~~ 6.9% (w/v) sodium chloride solution or equivalent.

**[0015]** The preferred composition of the present invention consisting of  $4.2 \pm 0.2$ g sodium chloride and  $7.6 \pm 0.6$ g hydroxyethylstarch per 100ml.

5 **[0016]** In the composition, the said hydroxyethylstarch contains at least 10% hydroxyethylstarch with molecular weight of 25, 000--45, ~~000,000~~ atomic mass units (amu).

**[0017]** The said dextran has molecular weight of 40, 000--230, ~~000,000~~ amu, carboxymethylstarch has molecular weight of 30, 000--80, ~~000,000~~ amu,

10 PVP has molecular weight of 5, 000--700, ~~000,000~~ amu, condensed glucose has molecular weight of 8, 000--12, 000 amu; sodium alginate has molecular weight of 20, 000--26, 000 amu; pectin has molecular weight of 20, 000--40, 000 amu; pentahydroxyethylstarch is the product of DuPont Company (Pentastarch) with molecular weight of 264, ~~000,000~~ amu.

15 **[0018]** The said gelatin derivatives have molecular weight of 20, 000- 35, ~~000,000~~ amu, and are selected from urea--conjugated gelatin, modified liquid gelatin, oxidized polygelatin and degraded gelatin poly--peptide.

**[0019]** Conventional injections are selected from water for injection, physiological saline, balanced buffers, glucose solution, sodium lactate  
20 solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution.

**[0020]** The composition of the present invention is prepared ~~as~~according to the following procedure: dissolving 3--18g of total amount of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch,  
25 PVP, gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N--2--hydroxypropylacrylamide, ethylene epoxide--polypropylene glycol, pectin, mannitol, and pentahydroxyethylstarch in 100 ml of total volume of one injection or mixture

of several injections selected from water for injection, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution; then adding 1. 5g sodium chloride and 0—5.4g of one or more substances selected from  
5 sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate, and Tris; with the proportion described above, then mixing, and dissolving, to obtain the composition of the present invention.

**[0021]** The preferred technical embodiments are as follows: (i) preparation of  
10 hydroxyethylstarch: According to the proportion of 1:0. 8- 0. 875: 0. 04--0. 042 (w/v/v), corn starch or sorghum starch, and 95% ethanol, and 35--38% hydrochloric acid are mixed, the temperature is raised to 65--80 °C for hydrolysis of starch, 16% sodium hydroxide solution is added in proportion of 0. 6--0. 7: 1 (v/w) of stated solution versus starch. Then ethylene epoxide is  
15 added in proportion of 0. 35--0. 5: 1 (w/w) of ethylene epoxide versus starch, then the mixture is heated to 65--75°C to cause starch hydroxyethylation. (ii) Formulation of the composition: Appropriate volume of water is added, to prepare  $7.6 \pm 0.6\%$  (w/v) hydroxyethylstarch solution. Suitable amount of activated charcoal is added to discolor the solution through adsorption. After  
20 filtration, the pH is adjusted to 5. 5--7, and the total of  $4 \pm 0.2$ g of sodium chloride is added, A suitable amount of activated charcoal is added again for adsorption and discolor action. After ~~filtrated~~filtration through 0. 8-~~4~~10 ~~um~~um micro--porous filter, the preferred composition of the present invention is obtained.

25 **[0022]** The present invention is further illustrated in detail by the following examples.

Preparative example.

Preparation of hydroxyethylstarch.

**[0023]** 100g Corn or sorghum starch are mixed with 87ml of 95% ethanol and 4.2 ml of 35% hydrochloric acid. The temperature is raised to 70°C to hydrolyze starch then 60ml of 16% sodium hydroxide solution is added, then 45g epoxyethane is added, and the mixture is heated to 70°C to complete hydroxyethylation of starch. According to the formula and preparative method described above, hydroxyethylstarch with molecular weight of 25,000--45,000 amu is obtained.

10 **[0024]** Example 1.

Prepare according to the following proportion:

hydroxyethylstarch	7.6g
sodium chloride	4.2g
water for injection	added to 100ml

15 **[0025]** 7.6g hydroxyethylstarch are dissolved in 100 ml of water for injection. 0.5g of activated charcoal is added, and the mixture is heated at 90°C for 15 min under stirring. After filtration through an asbestos plate filter, 4.2g sodium chloride (purity pharmaceuticals use) are added, and dissolved with stirring. 0.5g activated charcoal is added, and the mixture is heated at 20 90°C for 10 min under stirring. After filtration through an asbestos plate filter and 0.8-1.2 μm micro-porous filter, ~~resulted, the resultant~~ filtrate is transferred into 250ml or 500-ml glass or plastic bottles (bags), ~~after.~~ After sealing the bottles or bags are 1.05 kg/cm<sup>2</sup> and 121-123 °C for 15--30min for sterilization, to obtain the pharmaceutical composition of the present 25 invention.

**[0026]** Example 2.

Prepare according to the following proportion:

dextran 9g  
hydroxyethylstarch 3g  
sodium chloride 1.5g  
sodium bicarbonate 3.4g  
5 physiological saline added to 100ml

**[0027]** ~~Above~~The above--mentioned dextran (produced by Shanghai Glucose Factory), hydroxyethylstarch (prepared according to preparative example) are dissolved in physiological saline, and adsorbed and discolored with activated charcoal according to the method stated in Example 1. Then the above--  
10 mentioned sodium chloride, sodium bicarbonate, are added in turn, and dissolved with stirring. ~~There after~~Thereafter, the obtained solution is discolored, filtered, sterilized and filled, to obtain the pharmaceutical composition of the present invention.

15 **[0028]** Example 3.

Prepare according to the following proportion:

polyvinyl--pyrrolidone (PVP) (produced by Bayer) 12g  
sodium chloride 2g  
sodium acetate 4g  
20 10% glucose solution added to 100ml

**[0029]** According to the method described in Example 22, except that dextran and hydroxyethylstarch is replaced by PVP, sodium bicarbonate is replaced with sodium acetate, and physiological saline is replaced with glucose solution, the composition of the present invention is obtained.

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**[0030]** Example 4.

Prepare according to the following proportion:

sodium alginate (produced by Nanning 18g

Pharmaceutical Factory, Guangxi)

sodium chloride 1.5g

water for injection. added to 100ml

5 **[0031]** According to the method described in Example 1 to prepare the above-mentioned formulation, thus obtaining the pharmaceutical composition of the present invention.

**[0032]** Example 5.

Prepare according to the following proportion:

10 pectin (produced by PLA No. 185 Hospital) 3g

Pentahydroxyethylstarch (produced by 4g  
DuPont Company)

sodium chloride 4g

mannitol 7g

15 2% sodium lactate lution added to 100ml

**[0033]** According to the method in described in Example 1, pectin Pentahydroethylstarch and mannitol are dissolved in sodium lactate solution, then sodium chloride is added and dissolved.

20 **[0034]** Example 6.

Prepare according to the following proportion:

condensed glucose (produced by southwest 7g  
No. 5 Pharmaceutical Factory Chongqing)

N-2-hydroxy propyl acrylamide 2g

25 sodium chloride 4.4g

water for injection added to 100ml

**[0035]** Using the method in Example 1, the pharmaceutical composition of the present invention is prepared according to the above mentioned formula.

**[0036]** Example 7.

Prepare according to the following proportion:

fructose (produced by Shanghai 5g  
5 No. 2 Reagent Factory)  
xylitol (produced by Liaoyang organic 4g  
Chemical Plant)  
sodium chloride 4.8g  
water for injection added to 100ml

10 **[0037]** Using the method in Example 1, the pharmaceutical composition of the present invention is prepared according to the above--mentioned formula.

**[0038]** Example 8.

Prepare according to the following proportion:

15 glycerin 2g  
lactose (produced by Shanghai 5g  
No. 2 chemistry Reagent Factory)  
sodium chloride 6g  
water for injection added to 100ml

20 **[0039]** Using the method in Example 1, the pharmaceutical composition of the present invention is prepared according to the above-mentioned formula.

**[0040]** Test I: Animal Experiment

From adult healthy hybrid dogs, regardless of sex, under local  
25 anesthesia, isolate femoral artery and femoral vein, then insert catheters respectively.

**[0041]** The arterial duct is connected to a CF--II model monitor of cardiovascular function [Shanghai approval document number: Hu--Yao- Qi--

Jian (Zhun)--97--221103] to monitor cardiovascular status. ~~Bleed these~~The dogs are bled to monitor cardiovascular status. ~~Bleed these~~The dogs are bled to an average arterial pressure (MAP) of 40--50 mmHg for a period of about 15 min. ~~Maintain this~~This blood pressure level is maintained for 1 hour, then  
5 ~~infuse~~ the product prepared in Example 1 is infused at the dose of 8 ml/kg.

**[0042]** ~~Monitor the~~The cardiovascular function and urine volume is monitored over 4 hours after infusion. In the following tables, the blood pressure and other indexes are expressed as percentage of their basal levels respectively, the unit of urine volume is ml/kg body weight/h.

Table 1

Comparison between the composition of the invention and whole blood in equal volume of recovery of Cardiovascular function in dogs with shock. [unit: % compared with respective basal level]

		after transfusion				
		30 min	1h	2h	3h	4h
Systolic pressure	<u>composition of the invention</u> equal volume of whole blood	75±4 (p<=0.01)	76±4 (p<=0.01)	77±4 (p<=0.05)	78±5 (p<=0.05)	79±5 (p<=0.05)
	<u>composition of the invention</u> equal volume of whole blood	67±5 (p<=0.01)	69±6 (p<=0.01)	73±4 (p<=0.05)	73±4 (p<=0.05)	77±7 (p<=0.05)
diastolic pressure	<u>composition of the invention</u> equal volume of whole blood	77±5 (p<=0.01)	79±5 (p<=0.05)	81±4 (p<=0.05)	81±5 (p<=0.05)	81±5 (p<=0.05)
	<u>composition of the invention</u> equal volume of whole blood	69±6 (p<=0.01)	73±8 (p<=0.05)	76±7 (p<=0.05)	76±7 (p<=0.05)	82±12 (p<=0.05)
average arterial pressure	<u>composition of the invention</u> equal volume of whole blood	76±4 (p<=0.01)	78±4 (p<=0.01)	79±4 (p<=0.05)	80±5 (p<=0.05)	80±5 (p<=0.05)
	<u>composition of the invention</u> equal volume of whole blood	68±5 (p<=0.01)	71±6 (p<=0.01)	74±4 (p<=0.05)	75±4 (p<=0.05)	80±8 (p<=0.05)
cardiac contractivity	<u>composition of the invention</u> equal volume of whole blood	77±5 (p<=0.01)	79±5 (p<=0.01)	81±4 (p<=0.05)	81±4 (p<=0.05)	81±5 (p<=0.05)
	<u>composition of the invention</u> equal volume of whole blood	69±6 (p<=0.01)	73±8 (p<=0.05)	76±7 (p<=0.05)	76±8 (p<=0.05)	82±12 (p<=0.05)
cardiac output	<u>composition of the invention</u> equal volume of whole blood	105±13 (p<=0.01)	106±14 (p<=0.01)	103±14 (p<=0.05)	106±12 (p<=0.01)	106±17 (p<=0.01)
	<u>composition of the invention</u> equal volume of whole blood	89±10 (p<=0.05)	83±18 (p<=0.01)	83±15 (p<=0.01)	88±23 (p<=0.01)	88±16 (p<=0.01)
end-diastolic volume	<u>composition of the invention</u> equal volume of whole blood	82±4 (p<=0.05)	82±3 (p<=0.01)	83±4 (p<=0.01)	84±3 (p<=0.01)	84±4 (p<=0.01)
	<u>composition of the invention</u> equal volume of whole blood	78±7 (p<=0.05)	78±9 (p<=0.05)	80±7 (p<=0.05)	82±8 (p<=0.05)	84±8 (p<=0.05)



Table 2

Comparison between composition of the invention and equal volume of whole blood

For urine volume in restoration stage in shocked dogs [unit: ml/kg/h]

	after transfusion			
	1h	2h	3h	4h
Composition of the invention	2.23±1.03	0.94±0.22	0.95±0.29	1.00±0.30
equal volume of whole blood	0.33±0.21	0.27±0.16	0.73±0.41	0.61±0.25
	(p<0.01)	(p<0.01)		(p<0.05)

[0043] The composition of ~~the Example 1~~ of the invention was administered to 48 patients in Hefei No. 105 Hospital, Anhui province. The total effective rate was 100%. Most patients, had the blood pressure raised, urine volume increased, and the limbs became warm during transfusion. ~~Several~~ In several patients whom ~~the~~ conventional drugs couldn't already reverse, the composition of the Example 1 ~~of the invention~~ begin to play its role 5-- 10minutes after infusion. The circulatory function of patients ~~has~~ recovered basically, (and there were no obvious clinical complications.

[0044] Test 3. Experiment of acute toxicity  
10 ~~when dogs were~~ Dogs given at 2.5 times the dosage for ~~human~~, humans showed no adverse effects ~~have been showed~~. At 5 times the recommended dosage, salivation and vomiting were seen in the dogs. At 3. 75 times the recommended dosage vomiting was seen without salivation in the dogs. All the above administered dogs survived more than 45 days. At 7. 5 times the  
15 recommended dosage ~~the~~ death occurred in the administered dogs, and focal hemorrhage was seen in the lungs as target organs.

[0045] The composition of the present invention could be infused through ~~vein~~ the veins at ~~the~~ a dose of 8 ml of the composition of the present invention per kg body weight. It could be used directly in treating and saving ~~the~~  
20 patients with shock, combined injuries or hematorrhea, etc in order, to reverse the physio--pathological status of patients and to obtain time for sequential treatment.

[0046] As compared with the prior art, the pharmaceutical composition of this invention has the following prominent features and improvement:

25 [0047] 1. Greatly decreased volume of transfusion: In general, the dose for most patients is 500 ml or less ~~than 500 ml~~. Even if the patients suffered from lethal hematorrhea, to infuse only 1/4 to 1/6 of volume of lost blood is enough. Thus, it could obviously decrease the incidence rate of tissue edema or

overload of the heart.

**[0048]** 2. Rapid curative effect just during 5-- 10 minutes after infusion, the hemodynamics has been improved significantly.

**[0049]** 3. Good efficacy. As Test 1 showed, the composition of the invention  
5 had better efficacy than that of equal volume of fresh whole blood. Moreover, although the composition of the invention has no oxygen- carrying action, but it could improve micro--circulation and general status to decrease oxygen consumption and to increase oxygen transport. Thus, at least 50% of blood transfused could be saved, ~~it~~which could mitigate the contradiction with short  
10 supply of blood, decrease the complications induced by blood transfusion, and reduce ~~obviously~~ the economic burden for the patients.

**[0050]** 4. Maintain once of efficacy for long time. As Test 1 showed, after infusion of the composition of the invention, the improvement of hemodynamics and general condition could be maintained more than 3--4  
15 hours, even if all other infusion and drugs were not administered.

**[0051]** 5. Unnecessary special condition for storage: The composition could be stored at room temperature, simply used infused intravenously or intraosseously and conveniently transported, without special devices and special vehicles.

**[0052]** 6. Unnecessary blood typing and cross match tests: It is suitable for  
20 ~~individual~~individuals with any blood type. Thus~~the~~, valuable time could be gained to rescue the wounded and patients.

**[0053]** 7. Wider uses: It could widely be used in the treatment of patients with shock of various types, brain trauma, burn, combined injuries,  
25 cardiogenic shock induced by myocardial infarction of right ventricle, hypotension induced by hemodialysis, biliary pancreatitis, cardiovascular intoxication induced by narcotic, hepatic echinococcosis, and patients under operation.

[0054] 8. Change of administration model: The composition of the invention could be infused drop by drop intravenously, instead of pushing so it could be conveniently used with less complications.

[0055] In general, as compared with prior therapy, the composition of the  
5 present invention possesses unique benefit and ~~theoretical~~-innovation, for  
treating and saving the wounded and patients, ~~so it is active significance.~~

## ~~Claims~~CLAIMS

1. A pharmaceutical composition comprising 1.5--6.9 % (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane, and 3~18 % (w/v) of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, polyvinyl--pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium, alginate, N--2- hydroxypropylacrylamide, ethylene epoxide-polypropylene glycol, pectin, mannitol, and pentahydroxyethylstarch; as well as the remainder of conventional injections, as long as sodium chloride is not less than 1. 5 % (w/v), and the concentration of sodium ion is not more than that of 6.9 % (w/v) sodium chloride solution or equivalent.

2. The pharmaceutical composition of Claim 1, wherein the composition contains  $4.2 \pm 0.2$ g sodium chloride and  $7.6 \pm 0.6$ g hydroxyethylstarch per 100 ml.

3. The pharmaceutical composition of Claim 1 or 2, wherein the conventional injections are selected from water for injection, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution.,

4. The pharmaceutical composition of Claim 1 or 2, wherein hydroxyethylstarch contains at least 10% hydroxyethylstarch with molecular weight of 25,000--45,000.

5. The pharmaceutical composition of Claim 1, wherein gelatin derivatives have molecular weight of 20,000~35,000, and are selected from

urea--conjugated gelatin, modified liquid gelatin, oxidized polygelatin and degraded gelatin polypeptide.

6. The pharmaceutical composition of Claim 1, wherein dextran has molecular weight of 40,000--230,000; carboxymethylstarch has molecular weight of 30,000--80,000, PVP has molecular weight of 5,000--700,000, condensed glucose has molecular weight of 8,000~ 12,000, sodium alginate  
5 has molecular weight of 20,000--26,000, pectin has molecular weight of 20,000~40,000; pentahydroxyethylstarch has molecular weight of 264,000.

7. A method for preparing the pharmaceutical composition of Claim 1, comprising: dissolving 3--18g of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, PVP, gelatin derivatives, condensed glucose, glucose. fructose, lactose, glycerin, xylitol, sodium  
5 alginate, N--2--hydroxypropylacrylamide, ethylene epoxide-polypropylene glycol, pectin, mannitol, and pentahydroxyethylstarch, in total of 100 ml of one injection or mixture of several injections selected from water for injection, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and  
10 sodium chloride solution; the adding 1.5g sodium chloride and 0--5.4g of one or more substances selected from sodium chloride. sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate, and Tris with the proportion described above, then mixing, dissolving, to obtain the composition of the  
15 present invention.

*add C3*

~~Abstract~~ABSTRACT

The present invention relates to a pharmaceutical composition and the method for the preparation thereof, The composition comprises 1.5~ 6.9% (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, and the like, and 3~ 18% (w/v) of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, polyvinyl--pyrrolidone, gelatin derivatives, and the like as well as the remainder of conventional injections, as long as sodium chloride is not less than 1.5% (w/v). The pharmaceutical composition of the present invention is used to treat and save the wounded and patients, as well as to treat shock, its advantages include safe and convenient use, rapid and good curative effect, long time maintenance, extensive uses and the like.